SmithKline Beecham
Pharmaceuticals

August 30, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 99D-1454; Draft Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products; Chemistry, Manufacturing and Controls Documentation; Availability Federal Register, Wednesday, June 2, 1999 (64FR29657)

Dear Sir/Madam:

The draft guidance, according to the Notice issued at the time of the publication is intended to provide guidance for industry on the chemistry, manufacturing, and controls (CMC) documentation to be submitted in new drug applications (NDA's) and abbreviated new drug applications (ANDA's) for nasal spray and inhalation solution, suspension, and spray drug products. The draft guidance also covers CMC information recommended for inclusion in the NDA's or ANDA's regarding the components, manufacturing process, and associated controls with each of these areas.

GENERAL COMMENTS:

A careful analysis of the draft guidance shows that there is not significant regulatory relief embodied in these proposals, these proposals in fact add significant numbers of additional new requirements for the sponsor. On balance the reporting burden under the draft guidance would not be reduced but rather would be substantially increased.

Given the intent of the Modernization Act one would have expected the accompanying draft guidance to have included new opportunities for reduced reporting requirements. However this is not the case. Some of the key areas in the guidance include increased reporting requirements for specifications for the drug product and container-closure systems.

99D-1454

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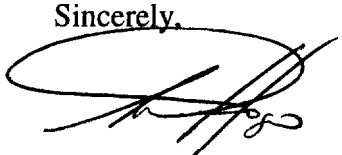
1250 S Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989 Telephone (610) 917 7000 Fax (610) 917 7707.

SmithKline 3eecham recommends that the implementation of the draft guidance be postponed in order to allow further development. Further, as these proposals move forward SmithKline Beecham would strongly encourage the FDA to work in collaboration with the industry in crafting improved versions of these draft guidance .

Detailed specific comments on the draft guidance are attached.

Sincerely.



Thomas M. Hogan
Director
North America Regulatory Affairs

Attachment

SB Comments on:
Draft FDA Guidance "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products" (Docket No. 99D-1454)
Table of Specific Comments
August, 1999

Section	Guidance Line	Comment	Rationale
III. DRUG PRODUCT B. Composition	142-149	Clarify the statement that "Any calculated excess for an ingredient....should be included only for justified reproducible manufacturing losses"	As the statement stands, it would appear to rule out stability overages.
III.C.1. Specifications for the Active Ingredients	180-190	The proposal that for suspension formulations, the active ingredient specification should include controls for crystalline form, amorphous content and foreign particulates may be difficult and/or unnecessary to comply with.	Depending upon the material, amorphous content may be difficult to assess and/or quantify. There should not be a blanket requirement. In certain cases, a control on amorphous content may be important. It should appear on the specification only if warranted. No information is provided on what is envisaged by a 'foreign particulates' test, its scope, and what limits would be considered reasonable.
III.C.2. Excipients	233-237	Clarify USP/NF specifications "may not be adequate...and should be supplemented, as appropriate"	Statement is not well defined.
III.C.2. Excipients	239-243	For excipients in suspension, "particle size, crystal form, amorphous content & foreign particulates should be considered".	Same comment as III.C.1. above.
III.C.2. Excipients	214 - 282	It is not clear whether this section applies only to oral inhalation products or whether some elements also apply to nasal sprays.	
III.E. Method of Manufacture and Packaging	292-293	All inhalation products "should be manufactured as sterile products".	Statement is too broad and not well defined.

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III.E. Method of Manufacture and Packaging	330 - 335	For inhalation products packed in plastic, "labelling by embossing or debossing is recommended to avoid the potential ingress of leachables.. . . If labels are used, absence of leachables should be demonstrated."	Is labeling by embossing/debossing feasible? Leachables should only be an issue if they pose a safety hazard. Requiring 'absence' penalises the sponsor for developing sensitive methodology.
III.F. 1. Specifications for the Drug Product: Nasal Sprays	349 – 616	Twenty tests are recommended. Many are tests one would normally associate with development pharmaceutics, establishing satisfactory product characteristics, but not part of the specification. One or two are noted as being applicable on stability or only required when the product is changed, but the inference is that the vast majority should be on the product specification and therefore potentially tested on every batch.	The proposals are unreasonable and in many cases specific tests will be unnecessary or irrelevant to a properly developed product. They introduce an unnecessary additional overhead to the manufacturing operation. The guidance should be modified to make it less prescriptive.
III.F. 1 .a. Appearance	364-367	Clarify "If any color is associated with the formulation. . .a quantitative test with appropriate acceptance criteria should be established"	What constitutes colour? Off-white? Why is this test required in all cases? Such testing: & limits should be applied only where warranted – where it adds value.
III.F. 1 .b. Identification	371-375	Chromatographic retention time alone is not an adequate method	Why not? When coupled with the GMP system and when a quantitative assay is also a requirement on the specification, it is surely adequate except when a closely related substance may be confused.
III.F. 1 .d. Impurities and Degradation Products	388 – 395	Please clarify if this section implies drug substance impurities require listing and limitation on the drug product specification.	Where drug substance impurities are limited on the drug substance specification, there should be no need to specify them on the drug product specification unless they are also degradation products.

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III.F.l .g. Spray Content Uniformity	415 – 447	The first paragraph of this section should be rewritten.	The section is confusing. Assessment of formulation, process and pump is, arguably, development pharmaceutics rather than batch release. It is proposed as a specification test, but it talks about comparing "among batches of product". Also states a purpose to "ensure SCU within the same container", which the test cannot deliver as defined.
III.F.1.g. Spray Content Uniformity	**423-425**	Remove requirement for controls for actuation parameters.	This adds unnecessary complexity to the testing. Many modem valves are designed to actuate similarly irrespective of manner of depression.
III.F.1.g. Spray Content Uniformity	**435 – 447**	The proposed criteria do not allow for any misfires.	**A** single misfire will make it impossible to pass a batch no matter how much testing is carried out.
III.F. 1 .i. Spray Pattern & Plume Geometry	**482-483**	Spray pattern testing as described should not be mandatory "on a routine basis as a quality control for release of drug product". The guidance should indicate such testing where relevant rather than prescribing it.	This level of scrutiny may be completely irrelevant to the effectiveness of the product, particularly given the vagaries of administration, nasal clearance and intervening ciliary transport.
III.F.l .j. Droplet Size Distribution	**504**	This testing should not be mandatory on the specification. Testing where relevant rather than prescriptive guidance.	May not be relevant to some products. Since the device manufacturer will usually test the spray performance of every batch of devices, testing on the product could fall into the category of development pharmaceutics

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III.F. 1 .k. Particle Size Distribution (PSD)	515	This testing should not be mandatory on the specification. The wording around "control the complete distribution" should be reconsidered.	Draft FDA guidance on "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" proposes that PSD data should be obtained using an aerodynamic method (cascade impactor or liquid impinger). This sort of test is not necessary on the product specification. PSD should be generated initially as part of development pharmaceutics, monitored through primary stability testing and used subsequently as part of the validation of significant formula or process changes. The requirement for an aerodynamic method is 'over the top' for a nasal spray. It is practically very difficult to define reasonable PSD limits that "control the complete distribution".
III.F. 1 .m. Foreign Particulates	530	Please clarify the Agency's expectations in this area.	This is not a USP defined test and the guidance does not contain discussion of what form it might take.
III.F. 1 .q. Leachables	580 & G	From this section and those on extractables that follow in section G, the Agency would appear to applying stricter criteria to control of packaging additives than they do to impurities arising from the drug substances. There is no bottom limit for identificaiton, quantitation and control.	This represents an unnecessarily heavy burden on the sponsor and penalises the sponsor that develops more sensitive analytical methodology.
III.F. 1 .r. pH	593	Testing and acceptance criteria should only be required where relevant	pH can be a poor critereon to use, particularly for systems of low buffering capacity, e.g. normal saline.
III.F. 1 .s. Osmolality	598	Should only be required where relevant	

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III.G. Container Closure Systems	848 – 887	Information demands should be reduced.	The information requested is extremely detailed and the relevance of much of the detail can be questioned in the light of the comprehensive demands for information demonstrating performance of the product that are contained in other parts of the document. Many devices contain a large number small components. There is no differentiation between product contact components and other components.
III.G.2. Control Extraction Studies	889	The demands are unreasonable and should be reduced.	It should not be necessary to carry out such work on each component. Appropriate safety data for each contact material should be sufficient. Specific data should be unnecessary where suitability of the elastomeric material has already been established through a history of use..
III.G.3. Routine Extraction	924	This requirement should be removed.	It is completely unnecessary to carry such a complex set of studies repeatedly on every component of every batch of pumps received. The demand is unreasonable.
III.G.4. Acceptance Criteria	944	The information requirements are extremely burdensome and should be reduced.	The level of detail information demanded is burdensome and does not add value – limits for individual and total extractables for each component – irrespective of whether they are made from the same material and whether they are product contact parts. What value does specification of physicochemical parameters add? This is specialised data generated by the pump manufacturer. The sponsor should not be required (line 985) to verify this.

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III.H.1 .a. Test Parameters, Acceptance Criteria and Procedures	1008 – 1019	Please modify text to make the sense clearer	Is the sense to exclude or include the exceptions?
III.H. 1 .b. Test Intervals	1020 – 1030	The Agency should ensure that the guidance reflects the outcome of the latest ICH discussions of stability testing guidance.	
III.H. 1 .c. Container Storage Orientations	1032 – 1040	Guidance should allow identification of most appropriate orientation prior to generation of primary stability data.	To reduce complexity of primary stability studies.
III.H.1.d. Test Storage Conditions	1042	Can the Agency clarify if the sense of this is that they intend to change the status of accelerated testing in justifying expiration dating beyond available real time data?	The predictive value of accelerated stability studies will depend on the characteristics of the particular product under test, just as it does for all other product types. Nasal sprays should not be a special case
III.H. 1 .d. Test Storage Conditions	1057 – 1062	The paragraph on low RH storage conditions should be rewritten. It should reflect the recent ICH discussions of stability testing guidance.	It is not logical to simply replace all the standard ICI-I conditions with low RH conditions. The storage conditions should reflect a sensible rationale for the particular product. Water loss (or gain) is not the only issue. For example, certain substances will permeate out of a plastic pack faster at high RI-I than at low RI-I.
III.H.1.i. Expiration Dating Period	1119 – 1127	The requirement to use different batches of container closure components should be removed.	This is an unnecessary complication. It should only be considered if experience of the product warrants it.
III.H.2. Other Stability considerations	1131	Remove the word "Any" from the start of the paragraph.	It overstates the point.
IV.C. Temperature Cycling	1195	The suggested cycle is impractical and unrealistic.	
IV.G. Effect of Orientation	1237 – 1241	These studies are liable to be completely pointless in many instances. Only to be considered if relevant	Patient will be provided with instructions on how to use the product.

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IV.I. Profiling of Sprays	1261 – 1270	Tail off characteristics should only be required where relevant.	Tail-off characteristics are relevant to a product which supplies a given number of doses of a chronic treatment, but it is not relevant to a product, such as au anti-infective, which is given for a specific course of treatment.
IV.N. Photostability	1307	Studies should be performed if drug substance photostability indicates they are relevant.	

SPH32

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